Information in practice

Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data

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Abstract

Objective To look for evidence of a relation between antibiotic resistance and prescribing by general practitioners by analysis of prescribing at both practice and individual patient level.
Design Repeated cross-sectional study in 1995 and 1996.
Setting 28 general practices in the Ninewells Hospital laboratory catchment area, Tayside, Scotland.
Subjects reviewed 8833 patients registered with the 28 practices who submitted urine samples for analysis.
Main outcome measures Resistance to trimethoprim in bacteria isolated from urine samples at practice and individual level simultaneously in a multilevel model.
Results Practices showed considerable variation in both the prevalence of trimethoprim resistance (26-50% of bacteria isolated) and trimethoprim prescribing (67-357 prescriptions per 100 practice patients). Although variation in prescribing showed no association with resistance at the practice level after adjustment for other factors ($P = 0.101$), in the multilevel model resistance to trimethoprim was significantly associated with age, sex, and individual-level exposure to trimethoprim ($P < 0.001$) or to other antibiotics ($P = 0.002$). The association with trimethoprim resistance was strongest for people recently exposed to trimethoprim, and there was no association for people with trimethoprim exposure more than six months before the date of the urine sample.
Discussion Analysis of practice level data obscured important associations between antibiotic prescribing and resistance. The results support efforts to reduce unnecessary prescribing of antibiotics in the community and show the added value of individual patient data for research on the outcomes of prescribing.

Introduction

The increasing prevalence of drug resistant bacteria is a major public health problem throughout the world.[1] Prescribers and policy makers require more precise information about the relation between prescribing and resistance in order to analyse the consequences of prescribing decisions.[2]

In Britain national prescribing data are currently available only at the general practice level, and analyses of these data have shown a weak relation between trimethoprim prescribing and resistance.[3 4] Collection of data about individual patients is technically achievable but is more expensive to collect and analyse than practice level data. In addition, linking of information from multiple data sources and creation of databases containing patient specific information raises important issues of confidentiality.[5] The Copenhagen Recommendations identified the need for research to establish the added value of person specific databases that link prescribing to other clinical information such as antibiotic resistance in order to meet the challenges of data protection legislation in Europe.[6]

We recently reviewed the literature supporting an association between prescribing in primary care and drug resistance but have found no studies that directly compared the results of practice level and patient level data.[7] The aim of this study was to test the hypothesis that, in comparison with practice level data, analysis of individual patient data would reveal a much stronger association between antibiotic exposure and resistance.

Methods

Study population

The study population was drawn from adults resident in the Tayside region aged ≥35 years and registered with a general practitioner in the catchment area for Ninewells Hospital laboratory from January 1995 to December 1996 inclusive. The subjects were still alive in December 1996 or had died in Tayside during this period. The final study population was 166 000 subjects from 28 practices, which is roughly 44% of the population of the Tayside region.

Ethics and data protection

This study was done under a set of standard operating procedures governing the use of personal data for research in the Medicines Monitoring Unit (MEMO) of Dundee University and written after the Data Protection Act in 1998 and the recommendations of the Caldicott report for implementation of the act in the NHS. They have been reviewed by an external privacy advisory committee, established in 1999 and chaired by Professor Elizabeth Russell from Aberdeen. The procedures have been developed in partnership with NHS Tayside and approved by the three NHS Tayside Caldicott Guardians. Responsibility for university staff compliance with the procedures lies with the University Caldicott Guardian, appointed on the advice of the NHS Guardians in 2000. Our compliance has been externally audited twice, in 2001 and 2003.

Patient data were anonymised electronically with programs written by MEMO. Firstly, each patient's unique community health index (CHI) number was changed to a new unique number that did not include any identifiable data, such as date of birth. Secondly, identifiable variables were changed (for example, full date of birth changed to age to nearest two months, postcode changed to Carstairs deprivation code). Thirdly, any identifying

textual data (name, address, etc) and any other identifying codes such as general practice or pharmacy codes were removed or changed to an anonymised mapped code. Finally, the study protocol and all other associated documents were entered within a project management system. The study protocol was also registered with NHS Tayside's data protection officer and included in a list of studies for external audit. Once registered on the project management system, the protocol cannot be altered without approval by Tayside Research Ethics Committee and registration of the new protocol with the data protection officer.

Once the data are anonymised, legally they are not covered by the requirements of the Data Protection Act. However, it has to be possible to re-identify an individual for the purposes of research governance and feedback of important results to professionals and patients. Exemption from the need for written consent for studies that follow agreed standard operating procedures was given by the Tayside Research Ethics Committee and the NHS Caldicott Guardians. In addition, all citizens of Tayside are informed that their electronic health records may be used in teaching, audit, or research through a leaflet distributed to all general practices by NHS Tayside. The leaflet says that individuals can request in writing that their records are not used in this way and that their objections will be respected.

Additional information about MEMO's standard operating procedures, external audits, and anonymisation software is available on our website (www.dundee.ac.uk/memo) by following the link to "Confidentiality/Advisory Issues."

Antibiotic resistance

The Ninewells Hospital medical laboratory receives about 45 000 urine samples for analysis from general practices each year. We obtained data on culture and sensitivity tests of these samples electronically. We included samples from midstream urine collection but excluded catheter specimens. We identified samples with and without trimethoprim resistant Gram negative bacteria and linked this information to patient records by means of the CHI number[8] and so to our information on practice and patient characteristics.

Outcomes

At the practice level, the outcome was the proportion of patients within the practice with urine samples containing trimethoprim resistant bacteria, whereas we coded individuals as having either resistant or sensitive bacteria.

Practice characteristics

We obtained prescribing information from the prescription database of MEMO, as described in detail elsewhere.[8] Briefly, this database contains prospectively gathered information on all dispensed community prescriptions since 1 January 1993 and diagnostic and demographic data on all patients admitted to hospital in Tayside since 1980 (Scottish morbidity record 1 (SMR1)). Hence, it does not include hospital or dental prescribed antibiotics. After their encashment at Tayside pharmacies, the prescriptions are sent by the Common Services Agency to MEMO. There, menu driven software determines the CHI number from the details on the prescription. The date the prescription was written is recorded, and the individual drug code entered from a drug dictionary developed by the Prescription Services Division and mapped to the British National Formulary.[9]

We recorded other characteristics about each practice, including the number of general practitioners, the ratio of male to female doctors, the number of patients, fundholding status, number of urine samples sent for analysis, and the distance from Ninewells Hospital calculated from the practice postcode. We extracted the age and sex distributions for each practice from the MEMO database, and the distributions of Carstairs codes of social deprivation.[10]

Patient specific characteristics

These included age, sex, and Carstairs social deprivation category, number of urine samples sent, and prescribing of trimethoprim, other antibiotics, and a selection of other drugs as general prescribing indicators (hormone replacement therapy, oral contraceptives, benzodiazepines, and selective serotonin reuptake inhibitors).

Statistical methods

Practice level analysis

We analysed the practice level data using multiple logistic regression. The equation allowed for confounding and interaction to be examined among the independent variables. The variables considered were number of urine samples; number of general practitioners; proportion of male general practitioners; fundholding status (yes or no); distance of practice from Ninewells Hospital; proportions of patients prescribed trimethoprim, other antibiotics, benzodiazepines, hormone replacement therapy, oral contraceptives, and selective serotonin receptor inhibitors; proportions of population who were men, aged 60 years or more, and had high social deprivation scores. We fitted a full model allowing for all significant covariates along with trimethoprim prescribing. In order to combine 1995 and 1996 data, we used a generalised estimating equation (GEE) model with year as the unit of repeated measures (using SAS, version 8). We assessed the robustness of practice ranking by prevalence of trimethoprim resistance by means of a simulation method described by Marshall and Spiegelhalter.[11]

Simultaneous practice and person specific analysis

We used MLwiN software for analysis of resistance and prescribing in relation to practice level and patient level factors simultaneously. We tested for a quadratic relationship with age because antibiotic prescribing is greater in young children and elderly people.[12] We performed the analyses for the whole dataset with year as a fixed covariate to allow for possible practice and population changes over time. Only practices that existed in both years were included in these analyses.

Results

Practice level results

Of the 28 practices, 11 (39%) were fund holders in 1995 and 17 (61%) in 1996, and six (21%) had only male doctors. The practices' list sizes ranged from 1342 to 10 653. None of these differences in practice characteristics affected the results.

The total number of patients who submitted urine samples was 8833 (fig 1). There was considerable variation between practices in the prevalence of trimethoprim resistance in Gram negative bacteria isolated from urine specimens (from 26% to 50%). There was similar variation in prescribing of trimethoprim (from 67 to 357 prescriptions per 100 practice patients) and of other antibiotics (from 2099 to 6352). However, apparent differences between practices and between years were not statistically significant, with considerable overlap of 95% confidence intervals (fig 2). Formal statistical analysis of practice rankings in 1995 and 1996 revealed that the 95% confidence intervals for most practices extended from first to last place. There was no relation

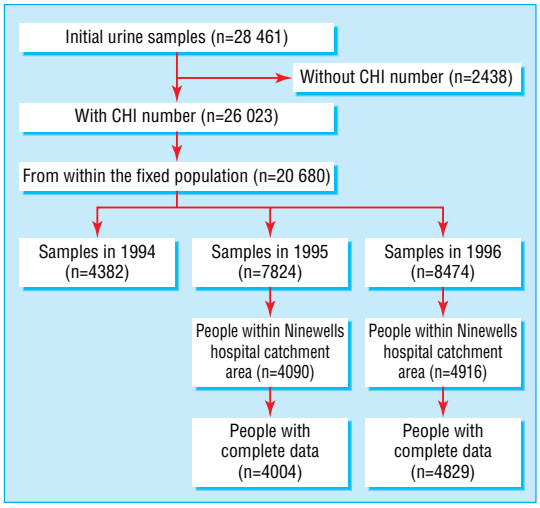

Fig 1 Flowchart for identification of individual subjects for patient level analyses from among those patients who had urine samples sent to Ninewells Hospital for analysis

between the number of urine samples sent by a practice and dispensing of trimethoprim or of other antibiotics.

The crude Spearman rank correlation between practice prescribing of trimethoprim and resistance was −0.039. In the multiple logistic adjusted analyses of practice level data from 1995 and 1996, the number of urine samples sent for analysis was positively associated with resistance (table 1). In addition, a high percentage of male general practitioners and high rates of prescribing oral contraceptives, hormone replacement therapy, and selective serotonin reuptake inhibitors were negatively associated with resistance. In the adjusted analysis trimethoprim prescribing was not significantly associated with trimethoprim resistance. No other variables were independently associated with trimethoprim resistance after adjustment, either with a stepwise procedure or with fitting a full model (table 1).

Multilevel modelling

In contrast to the practice level analysis, the simultaneous practice and individual level analysis showed many variables to be associated with trimethoprim resistance after adjustment, some highly significant. Older age and being female were both significantly associated with higher prevalence of resistance (table 2). Importantly, exposure to trimethoprim was strongly

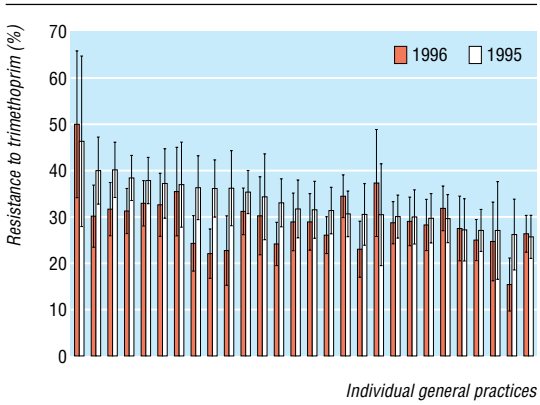

Fig 2 Prevalence of trimethoprim resistant bacteria in patients' urine samples by general practice (n=28). Practices are ranked in order of prevalence of resistance in 1995. (Error bars show 95% confidence intervals)

Table 1 Adjusted repeated measures model of the relation between prevalence of trimethoprim resistant bacteria in patients' urine samples and drug prescribing and other variables at the practice level (1995-6)

Variables	Odds ratio (95% CI)	P value
More trimethoprim prescriptions (+1000 scripts)	1.01 (0.99 to 1.02)	0.101
Greater percentage of male GPs (+10%)	0.95 (0.92 to 0.97)	<0.001
More urine samples sent for analysis (+100)	1.34 (1.26 to 1.40)	<0.001
More SSRI prescriptions (+1000 scripts)	0.67 (0.61 to 0.82)	<0.001
More HRT prescriptions (+1000 scripts)*	0.61 (0.50 to 0.82)	0.001
More oral contraceptive prescriptions (+1000 scripts)*	0.74 (0.61 to 0.99)	0.022

SSRI=selective serotonin reuptake inhibitor. HRT=hormone replacement therapy.
*Among female patients only.

associated with trimethoprim resistance (odds ratio 1.22 (95% confidence interval 1.16 to 1.28)). Exposure to other antibiotics was less strongly, but still highly significantly, associated with trimethoprim resistance (odds ratio 1.18 (1.06 to 1.32)). There were no significant associations for practice level variables with resistance after allowing for patient level factors; in fact, the variability of resistance due to practice level factors was negligible. There were some differences in the results for 1995 and 1996, resulting in significant interactions by year. No other variable was significantly associated with trimethoprim resistance in the combined data (table 2), but hormone replacement therapy was weakly associated with trimethoprim resistance (P = 0.028).

In our analysis, exposure to antibiotics always preceded resistance. In case-control studies this can lead to sampling bias due to sending only urine sample from patients who have not responded to initial antibiotic treatment. Although not a case-control design, we analysed the odds ratio of trimethoprim

Table 2 Multilevel model of the relation between presence of trimethoprim resistant bacteria in individual patients' urine samples and drug prescribing and other variables at the practice level and the patient level (1995-6)

Variables	Odds ratio (95% CI)	P value
Patient level factors		
Older age (+10 years)	1.15 (1.13 to 1.17)	<0.001
Year (1996 *v* 1995)	2.68 (2.14 to 3.35)	<0.001
Sex (male *v* female)	0.70 (0.59 to 0.82)	<0.001
Sex × year	1.42 (1.11 to 1.82)	0.005
Carstairs deprivation score	0.99 (0.97 to 1.00)	0.096
More urine samples sent for analysis (+1)	1.04 (0.99 to 1.10)	0.106
More trimethoprim prescriptions (+1)	1.22 (1.16 to 1.28)	<0.001
More prescriptions of other antibiotics (+1)	1.18 (1.06 to 1.32)	0.002
Benzodiazepines prescriptions (yes *v* no)	1.12 (0.68 to 1.83)	0.658
SSRI prescriptions (yes *v* no)	0.67 (0.34 to 1.32)	0.249
HRT prescriptions (yes *v* no)*	0.79 (0.64 to 0.97)	0.028
Oral contraceptive prescriptions (yes *v* no)*	1.01 (0.82 to 1.23)	0.954
Practice level factors†		
Medium practice size (*v* small)	1.05 (0.90 to 1.22)	0.552
Large practice size (*v* small)	1.09 (0.93 to 1.27)	0.282
Greater percentage of male GPs (+10%)	0.87 (0.65 to 1.18)	0.381
Fundholding practice (yes *v* no)	0.96 (0.84 to 1.09)	0.545

SSRI=selective serotonin reuptake inhibitor. HRT=hormone replacement therapy.
*Among female patients only.
†Practice effect μ_{1j}=0.007 (SE 0.006)

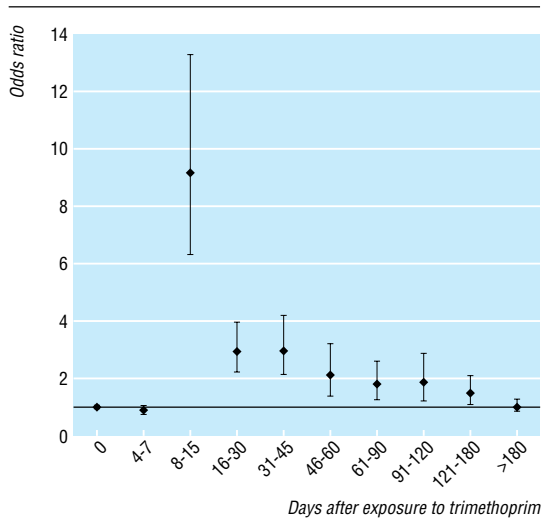

Fig 3 Odds ratio (95% confidence interval) of trimethoprim exposure in patients with trimethoprim resistant bacteria in urine versus those with sensitive bacteria by days after exposure to trimethoprim

exposure for patients with trimethoprim resistant bacteria by the number of days between trimethoprim exposure and submission of the urine sample (fig 3). This analysis showed that patients with trimethoprim resistant bacteria were more likely to have been exposed to trimethoprim up to six months before the date of the urine sample: odds ratio 9.19 (6.35 to 13.3) for trimethoprim exposure 8-15 days before the urine sample date, declining sharply to 2.93 (2.20 to 3.89) for exposure 16-30 days before and then steadily to 1.45 (1.03 to 2.05) for exposure 121-180 days (4-6 months) before. There was no association between trimethoprim resistance and exposure to trimethoprim more than 180 days (6 months) previously (odds ratio 1.00 (0.82 to 1.23)).

Discussion

We found a strong association between antibiotic prescribing and resistance at the individual patient level that was obscured by analysis of aggregate level data from the same population. A key conclusion is that aggregate level studies should not be used to assess the impact of changes in prescribing on resistance. Secondly, every time an antibiotic is prescribed in the community it increases the risk to the individual patient of colonisation by drug resistant bacteria. Thirdly, our results provide important supporting evidence for initiatives to achieve universal electronic prescribing in the NHS, showing the added value of analysis of prescribing data at the individual level.

Comparison with other studies

We found no relation between antibiotic prescribing and resistance at the general practice level. A systematic review of the literature about trimethoprim resistance and primary care prescribing from 1980 to 2000 identified five studies with area level data, of which only one found a significant relation.[13] A subsequent study of 371 practices in England reported a weak relation between trimethoprim prescribing and resistance (Spearman's rank correlation 0.24).[4] Six case-control studies published before 2001 all showed a strong relation between trimethoprim prescribing and resistance but had inadequate control for population differences in demographics.[13] This review did not include the results of a large case-control study in the Tayside population from 1993 to 1994, which confirmed a strong relation between trimethoprim resistance and prior exposure to trimethoprim or other antibiotics after controlling for other variables.[14]

We found only one other example of a parallel analysis of individual level data and aggregated data about prescribing and resistance.[15] This study, of 35 423 hospital inpatients, reported significant increases in prescribing of antibiotics over a four year period without any apparent change in the prevalence of resistance. However, multiple proportional hazards regression analysis revealed that exposure to a fluoroquinolone, third generation cephalosporin, ampicillin-sulbactam, or imipenem was a strong risk factor for colonisation with bacteria resistant to these drugs.[15]

Implications of results

The discrepancy between results with individual level data and aggregated data about antibiotic prescribing and resistance is probably largely due to the ecological fallacy.[16] Ecological studies about exposure and outcome are valid only if differences in exposure at the population level accurately reflect differences in exposure to all of the individuals within the populations. With respect to prescribing, large variations in the average consumption of drugs by populations are the product of much greater variation in exposure within the population, and ecological studies of exposure and outcome are therefore fundamentally flawed. Additional problems with aggregated data on prescribing and resistance include sampling bias and inability to control for confounding.[7] Nonetheless, very large ecological studies may reveal associations between antibiotic prescribing and resistance at the population level,[17] and one study suggests that historical antibiotic use in a hospital department and exposure of individual patients to antibiotics are both independent risk factors for infection by drug resistant bacteria.[18]

Our results show that isolation of trimethoprim resistant bacteria from urinary samples was not associated with trimethoprim exposure more than six months before the sample was taken. There is relatively little published information about the persistence of antibiotic resistant bacteria in the human intestinal flora.[19 20] Our cross sectional study suggests that the influence of trimethoprim prescribing reduces with time, but this needs to be confirmed in longitudinal cohort studies. Most of the available evidence comes from animal studies, which show that resistance persists long after exposure to the antibiotic has ceased, in part because of selective pressure exerted by completely unrelated antibiotics.[21 22] Human cohort studies have shown associations between antibiotic exposure and colonisation or infection by drug resistant bacteria, both in the community[23–25] and in hospitals.[26 27] At the population level we know that resistance to individual antibiotics persists in humans long after withdrawal of these drugs from clinical practice,[28 29] but these results are explained by selection by related antibiotics that are still in use. We need more information from longitudinal human studies at the individual level[30] to understand how the process of intestinal colonisation and persistence can be influenced by antibiotic control and by other measures.[31] The ability of primary care computing systems to produce high quality, patient specific data is increasing in Britain and elsewhere,[32] though the use of data may be restricted by legislation.[33]

Conclusion

Our results support efforts to reduce unnecessary prescribing of antibiotics in the community.[34] Clear demonstration of the added value of individual data will be important in the debate about practical and reasonable methods for obtaining consent for record linkage research.[35 36]

What is already known on this topic

UK national prescribing data are usually available only at the practice level, and analysis of these data has shown a weak relation between antibiotic prescribing and drug resistance in infective organisms

Such analyses probably suffer from ecological bias, which arises when area level data obscure important associations between individual exposure and risk

What this study adds

At the practice level, there was no association between variation in antibiotic prescribing and resistance after adjustment for practice level factors such as fundholding status

Inclusion of individual prescribing data in a multilevel model revealed a highly significant association between exposure to trimethoprim or other antibiotics, particularly in the previous six months, and resistance to trimethoprim

These results show that recent antibiotic exposure increases the risk of colonisation or infection by drug resistant bacteria and show the added value of analysis of data about individual patient prescribing

MEMO is a member of the MRC Health Services Research Collaboration.

Participators: PTD designed the statistical analysis, wrote the grant application, supervised LW, and wrote the first draft of the paper. LW carried out the statistical analysis and commented on the paper. DTS, GP, RC, AN, FMS, and TMM were involved in designing the study, collecting data, interpreting results, and re-drafting the paper. PGD designed the study, cowrote the grant application, and paper and is guarantor for the study.

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Competing interests: TMM serves on advisory boards for Pfizer, Pharmacia, and Novartis but none relating to the current topic. PGD serves on advisory boards about antibiotic prescribing and resistance for Aventis and Pharmacia.

Ethical approval: The study protocol was approved by Tayside Research Ethics Committee.

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